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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	46

DATE MAILED: 03/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,291	KRAMMER ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11 and 13-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,4,5,13 and 14* is/are allowed.

6)☒ Claim(s) *6-11,15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

This Office Action is a response to the "Amendment..." filed 10 January 2003 (Paper No. 16) in reply to the Non-Final Office Action mailed 8 October 2002 (Paper No. 13). Claims 1-12 were considered in Paper No. 13. Claims 1, 2, 4 and 6-11 were amended, claims 13-26 were added and claims 3 and 12 were cancelled in Paper No. 16. Claims 1, 2, 4-11 and 13-26 are pending and under consideration herein.

Priority

Receipt of the Corrected Filing Receipt and substitute Declaration indicating the filing date of the foreign priority document as 16 October 1998 are acknowledged. The application is now afforded priority to the German application DE 198 47 779.1.

Response to Amendment

Rejection of claims 3 and 12 is rendered moot by cancellation of the claims in Paper No. 16.

Specification

The disclosure stands objected to for reasons of record in Paper No. 13.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent

Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

The Amendments to the specification fail to provide SEQ ID NO for every referenced sequence. For example, the sequence set forth in the figures is not identified by SEQ ID NO in the brief description of the drawings. Applicant should review the disclosure and provide SEQ ID NO's for each sequence set forth therein.

Claim Rejections - 35 USC § 101

Rejection of claims 1-3 under 35 U.S.C. 101 is withdrawn in view of the amendments to the claims.

Rejection of claims 6-9 under 35 U.S.C. § 101 for failing to set forth process steps and thus improperly defining a process is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

Rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as lacking adequate written description is withdrawn in view of the amendments to the claims.

Claims 11 stands rejected and claims 24-26 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record in Paper No. 13 and herein below in the "Response to Arguments".

Rejection of claims 6-9 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to set forth positive process steps is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 2, 4, 5 and 10 under 35 U.S.C. 102(a) as being anticipated by Müller *et al.* (1998) is withdrawn in view of the perfection of the claimed priority to the German application DE 198 47 779.1 filed 16 October 1998.

Rejection of claims 1, 2 and 4 under 35 U.S.C. 102(b) as being anticipated by Rudert *et al.* (1995) is withdrawn in view of the amendments to claims 1 and 2.

Claim 10 stands rejected under 35 U.S.C. 102(b) as anticipated by Fulda *et al.* (1997) 57:3823-3829 for reasons of record in Paper No. 13 and herein below in the "Response to Arguments".

Response to Arguments

Claim 11 stands rejected and newly added claims 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has amended claim 11 such that the claim no longer specifically recites that the influence takes place on the basis of therapy and implies in the remarks that the claim is no longer directed to a therapeutic use. However, the amended claim 11 is still directed to a method of influencing apoptosis wherein the influence takes place on the basis of a diagnosis. Thus, the claim clearly encompasses a method of treatment because it sets forth diagnosis as the reason for the influencing step. The same is true for claim 26, which is directed to the process of claim 23 wherein the influencing step takes place on the basis of diagnosis. Claims 23 and 24 are directed to the process for influencing apoptosis set forth in claim 23 wherein the influencing takes place on the basis of a therapy and therefore clearly encompass the subject matter indicated as non-enabled in the previous office action.

In response to the rejection, Applicant first asserts, "the present disclosure provides sufficient guidance to enable one skilled in the art to use, without undue experimentation, the p53 antigen binding regions of the present invention. For instance, applicants recognize that not all cells express p53 either due to the lack of a cell-derived p53 or that the p53 is no longer capable of inducing apoptosis. In light of this recognition, the present specification provides sufficient guidance to determine if a tumor cell expresses p53. For instance, Example I set forth in the specification provides a method to determine if a tumor cell produces p53 with the ability to bind to the p53 binding regions according to the present invention. Once it is determined whether or not the tumor cell expresses p53, (Example IA) applicants provide guidance relating

to introducing an expression vector, which comprises an isolated p53 binding region of human CD95 receptor to influence apoptosis" (page 10).

This argument has been fully considered but is not found persuasive. First, it must be pointed out that the isolated p53 binding region has no ability to influence apoptosis in and of itself. The influence on apoptosis described in the instant application is a consequence of CD95 expression, which expression is regulated by the promoter sequence. Therefore, any teaching of a treatment comprising introducing an expression vector comprising the CD95 promoter sequence without a teaching of the protein or nucleic acid to be expressed by the expression vector is clearly not enabled because it fails to teach the therapeutically relevant component of the construct. The only expression constructs described in the instant disclosure comprise reporter genes operably associated with the promoter, which clearly would not influence apoptosis in any predictable way and are extremely unlikely to produce a therapeutic effect.

Applicant next states, [i]n example l(B) it was shown that if the tumor cell expresses p53, the p53 binding region according to the present invention responds more intensely to apoptosis induction." However, this result is obtained only because the promoter region is within the endogenous gene and operably linked to the CD95 coding region. In other words, the example cited does not even comprise a step wherein an expression vector is inserted into a cell. Furthermore, as pointed out in the previous office action, the claims encompass methods of treating any and all diseases wherein the p53 regulatory region of the CD95 receptor DNA is either activated or inhibited, yet Applicant has not pointed to a single example of successful treatment using the claimed method, and provides no details with respect to which conditions

might be responsive to this therapy, what inhibitory agent should be used, or how the agent should be administered.

Next Applicant states, "if the tumor cell does not express p53, Examples 2 and 3 provide guidance relating to introducing an expression vector comprising p53 and a p53 binding region of the presently claimed invention". Thus, Applicant appears to be suggesting that the claimed method encompasses gene therapy even though no gene therapy methods are set forth in the specification. Therefore the description of the claimed method is lacking necessary process steps such as introducing the p53 construct into a cell *in a patient*. In any case, the arguments set forth in the previous Office Action demonstrate that treatment according to the instant claimed method is unpredictable regardless of the means by which the p53 binding elements are activated (see the teachings from the prior art described in the paragraph bridging pages 7 and 8).

Finally, Applicant argues, "[t]o demonstrate the lack of enablement, the Office must demonstrate that one of skill in the art cannot, without undue experimentation, use the claimed isolated p53 binding regions to identify apoptosis-influencing substances". This argument is not persuasive because the rejected claims are not directed to a method of identifing apoptosis-influencing substances, but to methods of treatment.

Applicant's arguments fail to address the core issues of the outstanding enablement rejection, which are the absence of details with respect to which conditions might be responsive to the claimed therapy, what inhibitory agent should be used, or how the agent should be administered, as well as the inherent unpredictability of the claimed method, evidenced by the teachings of the prior art. Therefore, the claims stand rejected.

Claim Rejections - 35 USC § 102

In response to the rejection of claim 10 under 35 U.S.C. 102(b) as anticipated by Fulda *et al.* (1997) 57:3823-3829, applicant has amended the claim such that it depends from claim 1 and argues that because claim 1 recites specific sequences that are not disclosed in Fulda *et al.* claim 10 is not anticipated by Fulda *et al.*

This argument is not persuasive because the claim is directed to a process comprising activating the binding region of a CD95 receptor comprising the sequences set forth in claim 1. As those sequences were isolated from a human CD95 receptor promoter, and Fulda teaches activation of an endogenous human CD95 receptor promoter, the sequences of claim 1 would be inherent to the method of Fulda.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 and 15-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to methods comprising the following process steps:

-Claims 6-9: a) introducing a p53 binding region into a vector; b) transfecting a tumor cell with the expression vector; c) treating the tumor cell with a chemotherapeutic agent; and d) determining if the therapeutic agent influences apoptosis by measuring the level of living cell fraction.

-Claims 15 and 16: a) introducing a p53 binding region into a vector; b) transfecting a tumor cell with the expression vector; c) treating the tumor cell with a chemotherapeutic agent; and d) determining if the therapeutic agent influences apoptosis by measuring the level of tumor cell death.

-Claim 17, 18, 20 and 21: a) introducing a p53 binding region into a vector; b) transfecting a tumor cell with the expression vector; c) treating the tumor cell with a chemotherapeutic agent; and d) determining the level of apoptosis relative to a control tumor cell.

-Claims 19 and 22: introducing an effective amount of an expression vector comprising an isolated p53 binding region into a tumor cell to be treated in combination with a chemotherapeutic agent.

The disclosure teaches the following methods:

-Page 5, first full paragraph: a) introduce the p53-binding region in combination with a reporter DNA; b) add substances; c) select substances for transcription activating or transcription inhibiting effect;

-Example 1A: a) treat tumor cells with a chemotherapeutic agent; b) detect CD95 expression;

-Example 1B: a) treat tumor cells with a chemotherapeutic agent; b) treat cells with an anti-Apo-1 antibody; c) assay for the living cell fraction;

-Example 2: a) transfect cells with a construct comprising a nucleic acid encoding a wild-type p53 protein under the control of a constitutively active promoter; b) treat cells with a chemotherapeutic agent; c) detect CD95 expression; and

-Example 3: a) transfect tumor cells with an expression construct comprising a p53 responsive promoter operably associated with a reporter gene; b) detect reporter gene expression.

Methods comprising the method steps as set forth in the amended and new claims do not appear anywhere in the original disclosure. In particular, the originally filed disclosure does not describe a method wherein an expression vector comprising the p53 binding region of the claims is introduced into a tumor cell and that cell is assayed for cell death. The claimed methods thus add new matter.

Claims 6-9 and 15-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The limitations of the claims are set forth above. Given their broadest reasonable interpretation, the claims encompass methods of using a p53 binding region alone or operably linked to any and all genes for the purposes such as identifying apoptosis-influencing substances, or determining if a tumor cell responds to p53 induction. As pointed out herein above, the promoter sequences themselves would have no influence on apoptosis. Thus the outcome measured in the terminal step would be primarily dependent upon the gene operably linked to said promoter sequences. However, the disclosure does not teach a single expression construct that would be expected to be operative in the instant invention. The only constructs described comprise reporter genes which would not be expected to influence the outcome of the methods because they would not induce the apoptosis or cell death measured in the terminal step. The disclosure thus fails to teach the skilled artisan how the claimed method can be used to obtain practical information.

Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to methods of influencing apoptosis comprising introducing at least one p53 binding region of a CD95 receptor DNA according to claim 2 with p53. As claim 2 is directed to p53 binding regions "consisting of" short fragments of a promoter sequence, the claims encompass a method for influencing apoptosis comprising administering

fragments of DNA which have no activity unless comprised within a larger DNA molecule. The disclosure fails to teach how this method can be applied to a real-world problem.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite in the recitation of "the apoptosis-influencing substance comprises an induction or inhibition". Induction and inhibition are not appropriate modifiers for "apoptosis influencing substance". It would seem that applicant intends to limit the apoptosis-influencing substances to "inducers" or "inhibitors" and amending the claim accordingly would obviate this rejection.

Claims 8 and 9 are indefinite in being directed to a method of identifying apoptosis influencing substances wherein the influence takes place on the basis of diagnosis or therapy of diseases. It is unclear how a diagnosis would affect the influence of a substance on apoptosis. As the ability to influence apoptosis would be inherent to the substance, diagnosis would not affect that influence.

Allowable Subject Matter

Claims 1, 2, 4, 5, 13 and 14 are allowed.

The claims are directed to isolated promoter sequences, and vectors comprising said promoter sequences, which are free of the art of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 20, 2003

Anne-marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER